

**SNS COLLEGE OF PHARMACY AND HEALTH
SCIENCES
Coimbatore -641035**



**COURSE NAME: BP102T-PHARMACEUTICAL ANALYSIS (Theory)
I YEAR / I SEMESTER
SUB TOPIC: UNIT II-NON AQUEOUS TITRATION**

Design Thinking Concept in Pharmaceutical Analysis – Non-Aqueous Titration

Empathize: Understand the problem faced by analysts when weak acids or bases fail to ionize properly in aqueous titration.

Define: Identify the need for a new analytical method to achieve clear endpoints for weak organic compounds.

Ideate: Brainstorm possible non-aqueous solvents, indicators, and titrants to overcome solubility and ionization issues.

Prototype: Develop a non-aqueous titration using glacial acetic acid as solvent and perchloric acid as titrant.

Test: Perform titration using crystal violet indicator; observe sharp endpoint and improved accuracy and precision.

Non-Aqueous Titration – Mind Map

Solvents

- Protic (acetic acid)
- Aprotic (DMF, DMSO)

Acidimetry

- Used for weak bases
- Titrants: Perchloric acid in glacial acetic acid

Non-Aqueous Titration

Alkalimetry

- Used for weak acids
- Titrants: Sodium/potassium methoxide

Estimation

- Sodium Benzoate – titrated with perchloric acid
- Ephedrine HCl – titrated with sodium acetate/methoxide

NON AQUEOUS TITRATION:-

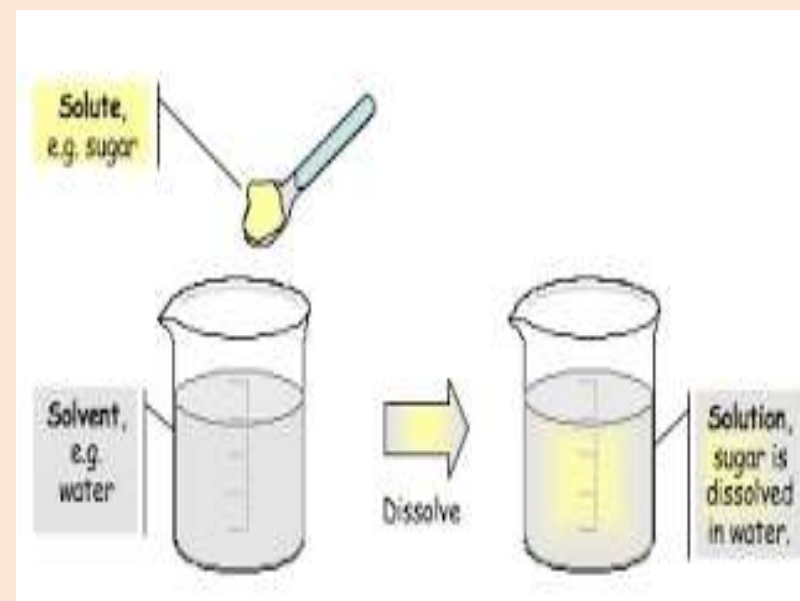
NON-AQUEOUS TITRATIONS HAVE THE FOLLOWING ADVANTAGES

- A non-aqueous solvent may help two or more acids in mixture. The individual acid can give separate end point in different solvent.
- Enlargement of solubility range: many substances that are not soluble in water can be easily titrated in water-free media (e.g. fats and oils) Enlargement of application range: weak bases and acids can be easily titrated.
- Substance compositions that cannot be separately determined in aqueous medium can often be titrated in non-aqueous media.
- Non-aqueous solvents are useful for the titration of very weak acids or bases that cannot be titrated in water.

Solvent which are used in non aqueous titration are called non aqueous solvent.

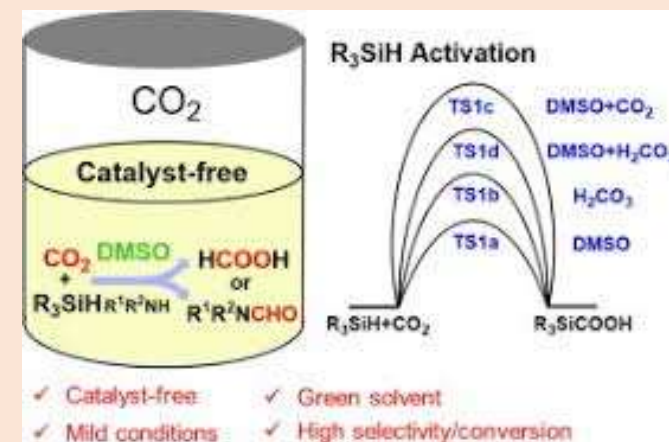
They are following types:-

- Aprotic Solvent
- Protogenic Solvent
- Protophilic Solvent
- Amphiprotic Solvent



Protogenic solvent:-

- A protogenic solvent is a solvent that can donate protons (H^+ ions) due to its ability to act as a Brønsted acid.
- These solvents are capable of protonating solutes, facilitating acid-base reactions.
- Examples include water, alcohols (e.g., methanol, ethanol), and acetic acid.
- They are often polar and can participate in hydrogen bonding.



Protophilic solvent:-

Protophilic solvents are basic in nature. Which possess a high affinity for proton.

Examples:-Liquid ammonia, amines and ketone



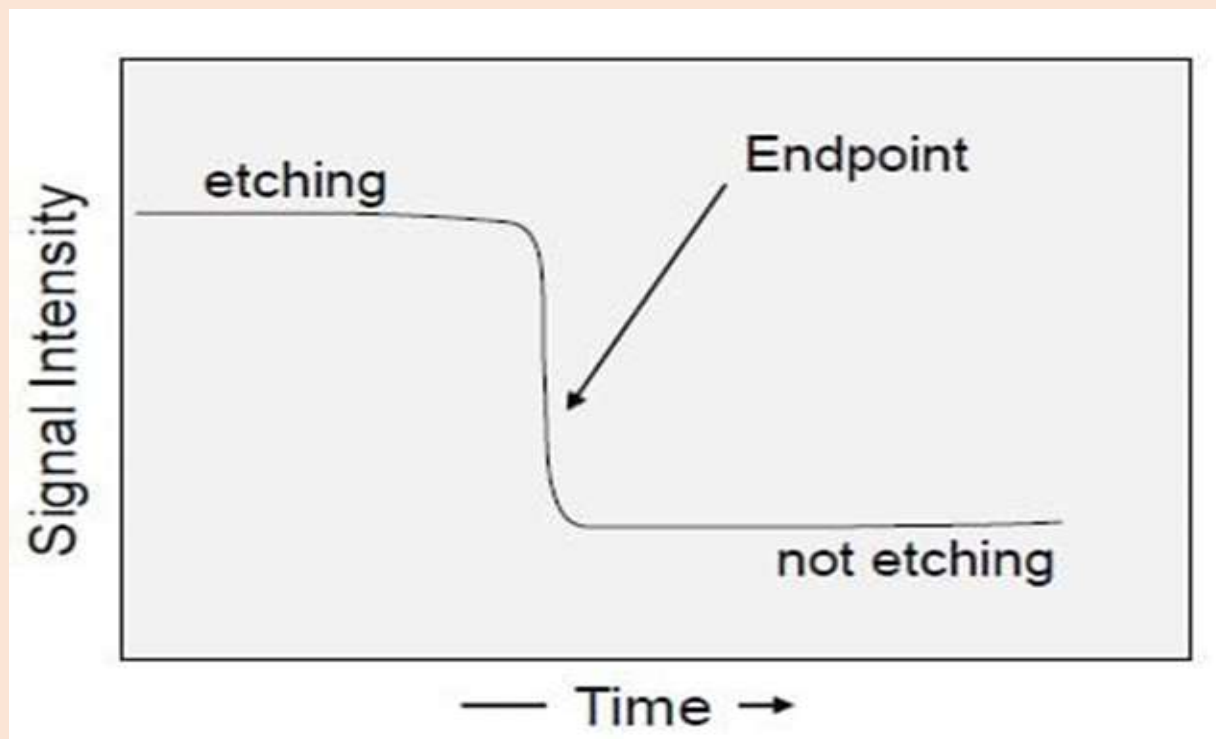
Amphiprotic solvent:-

Those solvent they work as both mean Protogenic or Protophilic. It means Amphiprotic solvent are acidic and basic in nature. And they are accept the proton and donate the proton.

For examples:-Water, Alcohols and weak organic acids.

Detection of end point:-

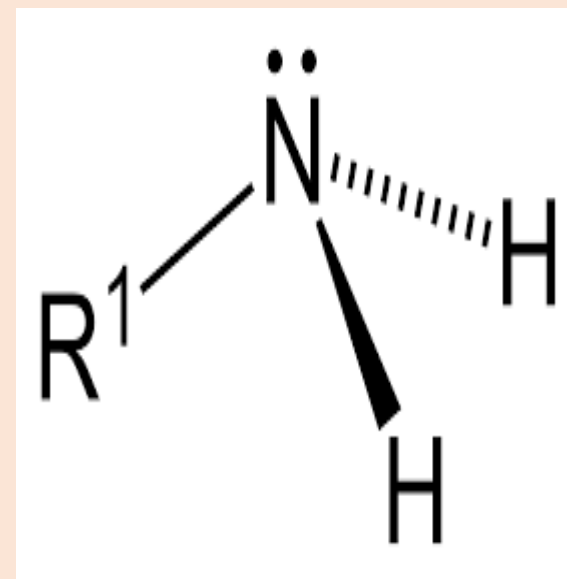
Visual indicator are formed to the most suitable for the detection of end point in non-aqueous titration.



ACIDIMETRY IN NON AQUEOUS TITRATIONS:-

METHODOLOGY:-

- I. Preparation of 0.1 N Perchloric acid.
- II. Standardization of 0.1 N Perchloric Acid.
- III. Choice of Indicators, and Effect of Temperature on Assays.
- IV. Titration.

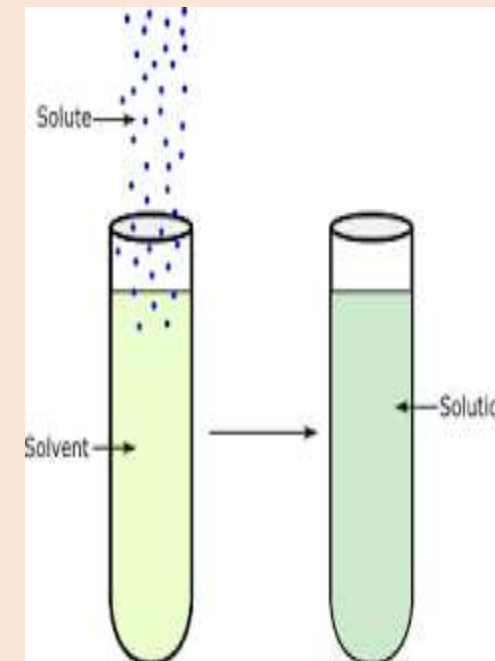


Precautions:-

1. Selection of Solvent:

Choose an appropriate solvent (e.g., glacial acetic acid, ethanol, or DMF) based on the analyte's properties (acidic or basic) to ensure solubility and proper endpoint detection.

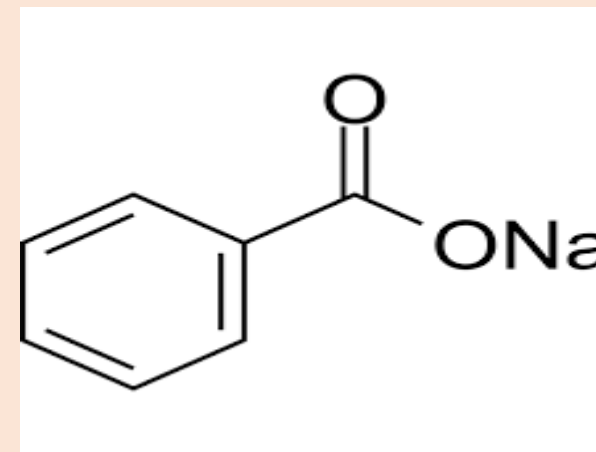
2. Use of Anhydrous Reagents: Use dry, high-purity reagents to prevent water contamination, which can weaken the titration response or cause side reactions.



Estimation of sodium benzoate:-

Principle:

Sodium benzoate ($\text{C}_6\text{H}_5\text{COONa}$) reacts with a strong acid (e.g., perchloric acid, HClO_4) in a non-aqueous solvent like glacial acetic acid, where it acts as a base. The reaction forms benzoic acid and a salt, allowing quantification by titration.



Titration: Add 2–3 drops of crystal violet indicator to the sample solution.

Titrate with 0.1 N perchloric acid solution from a burette until the color changes from violet to blue-green (endpoint).

Calculations:

The amount of sodium benzoate is calculated using the stoichiometry of the reaction. The molecular weight of sodium benzoate ($\text{C}_6\text{H}_5\text{COONa}$) is 144.11 g/mol.

Formula:

$$\text{Weight of sodium benzoate (g)} = \frac{V \times N \times M}{1000}$$

Where:

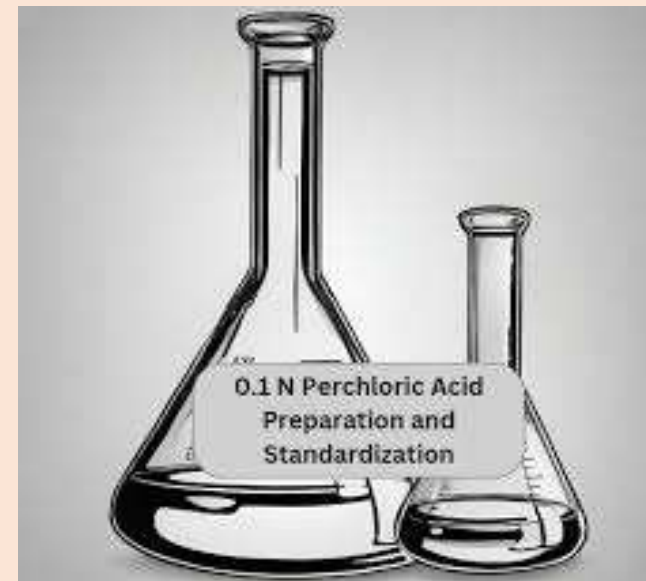
V = Volume of perchloric acid used (mL)

N = Normality of perchloric acid (e.g., 0.1 N)

M = Molecular weight of sodium benzoate (144.11 g/mol)

Percentage Purity:

$$\% \text{ Sodium benzoate} = \left(\frac{\text{Weight of sodium benzoate}}{\text{Weight of sample}} \right) \times 100$$



Ephedrine HCL:-

Principle:

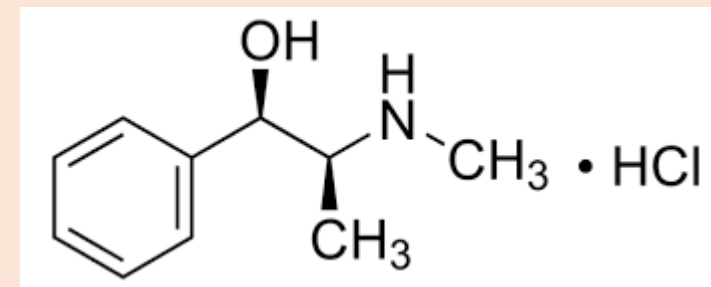
Ephedrine HCl ($C_{10}H_{15}NO \cdot HCl$) reacts as a base with a strong acid titrant (e.g., perchloric acid, $HClO_4$) in a non-aqueous solvent, forming ephedrine perchlorate and hydrochloric acid. The reaction allows quantitative determination of ephedrine HCl.



Reagents:

1.Sample: Ephedrine HCl (analytical grade or sample to be tested).

2.Solvent: Glacial acetic acid (to dissolve ephedrine HCl and enhance its basicity).



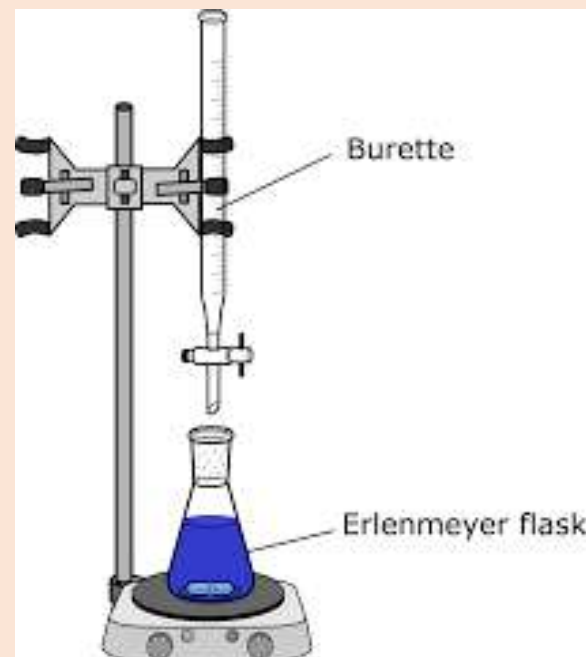
Procedure:

1. Sample Preparation:

1. Accurately weigh about 0.1–0.2 g of ephedrine HCl.
2. Dissolve in 20–30 mL of glacial acetic acid. Gentle warming may be needed for complete dissolution.

2. Titration:

1. Add 2–3 drops of crystal violet indicator to the sample solution.
2. Titrate with 0.1 N perchloric acid from a burette until the color changes from violet to blue-green (endpoint).
3. Alternatively, use a potentiometer to detect the sharp potential change at the endpoint.



Calculations:

The molecular weight of ephedrine HCl ($C_{10}H_{15}NO \cdot HCl$) is 201.69 g/mol. The amount of ephedrine HCl is calculated using the stoichiometry of the reaction.

Formula:

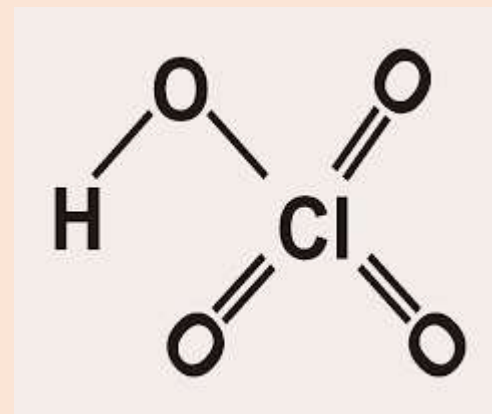
$$\text{Weight of ephedrine HCl (g)} = \frac{V \times N \times M}{1000}$$

Where:

V = Volume of perchloric acid used (mL)

N = Normality of perchloric acid (e.g., 0.1 N)

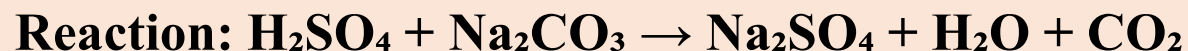
M = Molecular weight of ephedrine HCl (201.69 g/mol)



Percentage Purity:

$$\% \text{ Ephedrine HCl} = \left(\frac{\text{Weight of ephedrine HCl}}{\text{Weight of sample}} \right) \times 100$$

Standardization of Sulphuric Acid Solution:



Purpose: Determine the exact concentration of H_2SO_4 solution.

Method: Titration with a primary standard (e.g., sodium carbonate, Na_2CO_3) using methyl orange indicator.

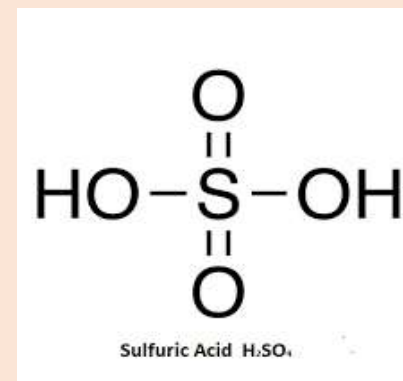
Procedure:

Pipette 10 mL of 0.1 N Na_2CO_3 into a conical flask.

Add 2-3 drops of methyl orange indicator (yellow in basic solution).

Titrate with H_2SO_4 solution until the color changes to red-orange (endpoint).

Record the volume of H_2SO_4 used.



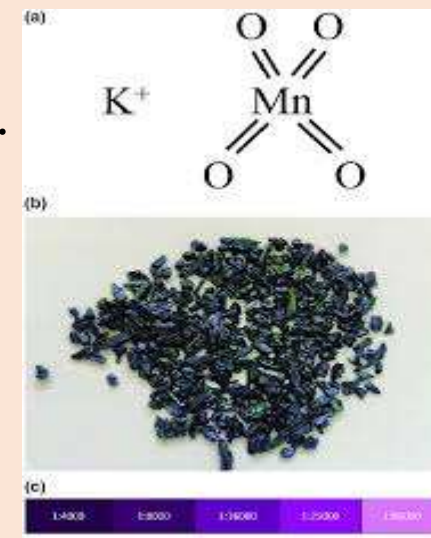
Preparation of Potassium Permanganate Solution:

Procedure for 0.1 M/0.5 N KMnO_4 Solution:

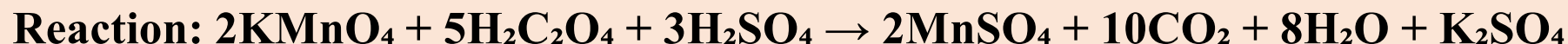
- Weigh 15.803 g of KMnO_4 crystals accurately.
- Dissolve in 500 mL of distilled water in a volumetric flask.
- Boil the solution for 15–20 minutes to remove organic impurities and stabilize.
- Cool and make up the volume to 1 L with distilled water; filter if necessary.

Precautions:

- Use distilled water free of reducing agents.
- Store in a dark bottle to prevent decomposition by light.
- Allow the solution to stand for 24–48 hours before use to ensure stability.



Standardization of Potassium Permanganate Solution:



Purpose: Determine the exact concentration of KMnO_4 solution.

Method: Titration with a primary standard (e.g., oxalic acid) in acidic medium.

Procedure:

1. Pipette 20 mL of 0.1 N oxalic acid ($\text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$) into a conical flask.
2. Add 10 mL of 2 N H_2SO_4 and heat to 70–80°C.
3. Titrate with KMnO_4 solution until a permanent pale pink color appears (self-indicator).
4. Record the volume of KMnO_4 used.

Calculation:

1. Normality of $\text{KMnO}_4 = (\text{Normality of oxalic acid} \times \text{Volume of oxalic acid}) / \text{Volume of } \text{KMnO}_4$.

Case Study:

“The Misjudged Titration of Weak Base” In Innovate Pharma Lab, analyst Aarav was assigned to determine the purity of Imipramine hydrochloride, a weak base, using non-aqueous titration. He initially used water as the solvent and titrated with 0.1 N HCl, but the endpoint was unclear — the color change was very faint, and his results were inconsistent. Later, his mentor Dr. Sneha explained that weak organic bases are poorly soluble and weakly dissociated in water, so non-aqueous solvents like glacial acetic acid should be used instead. Aarav repeated the titration using perchloric acid in glacial acetic acid and obtained sharp, consistent endpoints.

ASSESSMENT:

Choose the most appropriate answer.

1. Why was Aarav unable to obtain a sharp endpoint when he used water as the solvent?

- A. The reaction was too fast in water B. The base was weakly ionized in water
C. The acid was too strong for the base D. The indicator was inappropriate

2. Why are non-aqueous solvents like glacial acetic acid preferred in this titration?

- A. They act as strong oxidizing agents B. Better solubility and ionization of weak bases
C. They neutralize the base directly D. They have a strong color change

3. Which of the following is commonly used as a titrant in non-aqueous titration of weak bases?

- A. Sodium hydroxide B. Hydrochloric acid
C. Perchloric acid in glacial acetic acid D. Sulphuric acid in water

4. Which indicator would Aarav most likely use for this non-aqueous titration?

- A. Methyl orange B. Crystal violet
C. Phenolphthalein D. Bromothymol blue

5. After using the correct solvent and titrant, Aarav obtained sharp endpoints and consistent results.

What major advantage did non-aqueous titration provide?

- A. Reduced equipment cost B. Better control over temperature
C. Improved accuracy in determining weak acid/base purity D. Faster titration process

Reference:

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2. A.I. Vogel, Text Book of Quantitative Inorganic analysis.
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